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# Evaluation of pseudoexfoliation syndrome patients with systemic immune indexes

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## Abstract

**Purpose** The aim of this study was to investigate the level of peripheral blood systemic immune indexes in pseudoexfoliation syndrome (PXS) patients and to compare the results with healthy controls.

**Methods** This study included 143 healthy controls (group 1) and 100 patients (group 2). Peripheral blood samples were collected from all participants. Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), systemic immune inflammation index (SIII), systemic inflammation response index (SIRI), systemic inflammation modulation index (SIMI) and aggregate systemic inflammation index (AISI) were calculated.

**Results** According to complete blood count, leukocyte, monocyte and platelet counts showed a statistically significant difference between the two groups ($p < 0.001$ for all). Systemic immune indexes (NLR, PLR, SIII, SIRI, SIMI and AISI) in group 2 were statistically significantly higher compared to group 1 (PLR for $p = 0.011$, others $p < 0.001$).

**Conclusion** In conclusion, systemic immune indexes (NLR, MLR, PLR, SIII, SIRI, AISI and SIMI) were elevated in PXS patients compared to healthy controls. These indexes may serve as an easy, simple and cost-effective tool to assess the degree of systemic inflammation in patients, playing an important role in recognizing the underlying mechanisms of diseases and thus potentially guiding treatment.

**Keywords** Glaucoma, Pseudoexfoliation, Systemic immun inflammation index, Systemic inflammation modulation index, Systemic inflammation response index

## Introduction

Pseudoexfoliation syndrome (PXS) is essentially a systemic elastic microfibrillopathy. It affects many tissues and organs, particularly the ocular, cardiovascular and musculoskeletal system [1]. The prevalence of the syndrome has not yet been conclusively established, but it is common in Scandinavia [2]. One study reported a prevalence of 5.7% in the population over 40 years of age [3]. The distribution according to gender is variable due to the higher number of female in the elderly population [3, 4].

The formation of exfoliative material is due to the production, aggregation and abnormal cross-linking of microfibrils. Although many genes and enzymes have been identified in the pathogenesis of the disease, the underlying mechanism has not been completely clarified [5].

Systemic and local immune responses are involved in the development and progression of diseases. Recently, different systemic inflammation parameters (systemic immune inflammation index (SIII), systemic inflammation response index (SIRI) and aggregate index of

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systemic inflammation (AISI)), including neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), have been reported as prognostic factors in different diseases [6–8].

Neutrophils, monocytes and lymphocytes are elements of the immune system. The number of these cells in the peripheral blood increases due to inflammation. In addition to these parameters obtained by a simple complete blood count, systemic immune indexes obtained by a series of calculations are biomarkers of inflammation in the body.

A study investigating the role of inflammation in the pathogenesis of PXS shows that the profibrotic effect induced by increased transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF) locally activates fibrous tissue production in early PXS, prolongs the effect of PDGF in the late stage, and finally is predominantly controlled by epidermal growth factor (EGF) and insulin-like growth factor (IGF) in the advanced stage [9].

For these reasons, we investigated the levels of peripheral blood systemic immune indexes in PXS patients and compared the results with healthy controls.

## Materials and methods

The principles of the Declaration of Helsinki were followed throughout this study. The study population consisted of patients who were followed up for PXS in the Ophthalmology Clinic of Mersin City Hospital between January 2020 and November 2023.

### Study population

This study included 100 consecutive patients (group 2) aged between 40 and 90 years, without active local and/or any systemic inflammatory symptoms (such as fever, cough or red eye), without known primary/secondary glaucoma, anterior, intermediate and/or posterior uveitis, without any antiglaucomatous drops and with pseudoexfoliative material in at least one eye, and 143 healthy controls (group 1) with similar age and gender distribution.

All patients underwent a complete ophthalmologic examination with slit lamp biomicroscopy. The iridocorneal angle was evaluated with a three-mirror gonioscopic examination. Pupil dilation was performed with 0.5% tropicamide to detect pseudoexfoliative material on the pupillary margin and/or anterior lens capsule. All PXS patients (PXS and pseudoexfoliative glaucoma (PXG)) were included in group 2. Patients with previous intraocular surgery for any reason, systemic and/or local corticosteroid use, and colony stimulating factor use for any reason were excluded from this study.

### Data from this study

Age and gender of all participants were reported. Peripheral blood samples were collected from all participants. Complete blood count (leukocyte, neutrophil, lymphocyte, monocyte, eosinophil, basophil and platelet counts (x $10^9$/L)), C-reactive protein (CRP, mg/dL), ferritin (ng/mL) and haptoglobin (mg/dL) values were obtained from the collected samples.

### Systemic immune indexes

Neutrophil to lymphocyte ratio (NLR, unitless), platelet to lymphocyte ratio (PLR, unitless), monocyte to lymphocyte ratio (MLR, unitless), systemic immune inflammation index (SIII = (Platelet x Neutrophil) / Lymphocyte counts, $10^9$/L), systemic inflammation response index (SIRI = (Monocyte x Neutrophil) / Lymphocyte count, $10^9$/L) and aggregate systemic inflammation index (AISI = (Monocyte x Neutrophil x Platelet) / Lymphocyte count, $10^{18}$/L) were calculated. Systemic inflammation modulation index (SIMI) is a novel index that we defined in a previous study. It is calculated as SIMI = (Monocyte x Platelet) / Lymphocyte counts. The unit is $10^9$/L [10].

### Statistical analysis

Statistical Package for the Social Sciences (SPSS) 25.0.1 (IBM Co., NY, US) was used for statistical analysis of this study data. The normality of numerical variables with normal distribution was evaluated by Kolmogorov-Smirnov test. Normally distributed data were expressed as mean ± standard deviation and non-normally distributed data were expressed as median (quartile 1 (Q1)-quartile 3 (Q3)). Non-numerical variables were shown as number and percentage (%). Student t test and Mann Whitney U test were used for numerical data in the comparison of two groups. Chi-square test was performed for non-numerical variables. Receiver operating characteristic (ROC) curve analysis was performed to analyze the area under the ROC curve (AUC). For statistical significance, $p<0.05$ was chosen.

## Results

Eighty-six (60.1%) of 143 people in group 1 and 62 (62%) of 100 patient in group 2 were female. The mean age of group 1 was 55.2 ± 8.3 years, while the mean age of group 2 was 56.3 ± 8.4 years. The two groups were similar in terms of age and gender distribution ($p=0.549$, $p=0.770$, respectively). Of the 100 patients in group 2, 44 (44%) had unilateral and 56 (56%) had bilateral PXS. Body mass index (kg/$m^2$), comorbidities and smoking were not significantly different between the groups. The mean intraocular pressure (IOP) value in group 1 was 14.6 ± 3.5 mm Hg and 19.2 ± 6.6 mm Hg in group 2. The mean IOP value was statistically significantly higher in group 2 compared to group 1 ($p=0.016$). (Table 1)

**Table 1** Comparison of demographic data of the participants

| | Group 1 (Control) | | Group 2 (PXS) | | *p* |
|---|---|---|---|---|---|
| ***N*** | **143** | | **100** | | |
| Age (years) | 55.2 ± 8.3 | | 56.3 ± 8.4 | | 0.549 |
| Male (n,%) | 57 | 39.9 | 38 | 38.0 | 0.770 |
| Female (n,%) | 86 | 60.1 | 62 | 62.0 | |
| BMI (kg/m2) | 27.6 ± 5.92 | | 28.1 ± 6.24 | | 0.369 |
| DM (n,%) | 7 | 4.9 | 9 | 9.0 | 0.568 |
| HT (n,%) | 10 | 7.0 | 6 | 6.0 | |
| Smoking (n,%) | 8 | 5.6 | 7 | 7.0 | |
| IOP (mm Hg) | 14.6 ± 3.5 | | 19.2 ± 6.6 | | 0.016 |

IOP: Intraocular pressure, PXS: Pseudoexfoliation Syndrome, DM: Diabetes mellitus, HT: Systemic arterial hypertension, BMI: body mass index

**Table 2** Comparison of complete blood counts of the participants

| | Group 1 (Control) | Group 2 (PXS) | *p* |
|---|---|---|---|
| ***N*** | **143** | **100** | |
| Leucocytes ($10^9$/L) | 7.53 ± 1.71 | 9.9 (7.5–13.4) | < 0.001 |
| Neutrophils ($10^9$/L) | 4.23 ± 0.99 | 5.2 (3.6–8.4) | 0.087 |
| Lymphocytes ($10^9$/L) | 2.52 ± 0.40 | 2.92 (1.86–4.01) | 0.353 |
| Monocytes ($10^9$/L) | 0.49 ± 0.21 | 1.04 (0.69–1.43) | < 0.001 |
| Eosinophils ($10^9$/L) | 0.31 ± 0.10 | 0.18 (0.08–0.38) | 0.249 |
| Basophils ($10^9$/L) | 0.06 ± 0.03 | 0.06 (0.04–0.10) | 0.812 |
| Platelets ($10^9$/L) | 253.7 ± 96.0 | 364 (272–474) | < 0.001 |

PXS: Pseudoexfoliation Syndrome

**Table 3** Comparison of serum inflammatory biomarker levels of the participants

| | Group 1 (Control) | Group 2 (PXS) | *p* |
|---|---|---|---|
| ***N*** | **143** | **100** | |
| CRP (mg/dL) | 5.32 ± 1.44 | 7.8 (4.3–31.7) | 0.145 |
| Ferritin (ng/mL) | 163.7 ± 48.5 | 178 (56.1–344.3) | 0.253 |
| Haptoglobin (mg/dL) | 99.1 ± 37.6 | 104.8 ± 22.7 | 0.396 |

CRP: C-reactive protein, PXS: Pseudoexfoliation Syndrome

According to complete blood count, leukocyte, monocyte and platelet counts showed a statistically significant difference between the two groups ($p<0.001$ for all). (Table 2)

Serum inflammatory biomarkers (CRP, ferritin and haptoglobin) levels were not significantly different between the two groups. (Table 3)

Systemic immune indexes in group 2 were statistically significantly higher compared to group 1 (PLR for $p=0.011$, others $p<0.001$). (Table 4)

According to the results of ROC analysis, the areas under the curve (AUC) of all systemic immune indexes are shown in Fig. 1. All indexes showed a statistically significant increase in group 2 compared to group 1 (all, $p<0.001$). (Table 5)

## Discussion

Systemic immune indexes include several different cell types involved in the immune response, including neutrophils, lymphocytes and platelets, as well as monocyte counts. These indexes have been identified as biomarkers, particularly for predicting the course of diseases and their response to treatment. Systemic immune indexes determined by cell counts obtained from complete blood count and their combination have been investigated in many diseases in the literature. A meta-analysis by Shirvani et al. showed that NLR is a valuable marker of systemic inflammation and is significantly increased in many eye diseases, suggesting that it may play an important role in the pathophysiology of these diseases [11].

Two studies in retinal artery occlusion (RAO) patients also reported that NLR was higher in RAO patients [12, 13]. In two studies evaluating inflammation indexes in retinal vein occlusion (RVO) patients, leukocytes, neutrophils, NLR and SIII were significantly higher in RVO patients compared to controls. In these studies, SIII and NLR were identified as promising indicators for predicting the development of RVO [14, 15]. Studies in

**Table 4** Comparison of systemic immune indexes of the participants

| | Group 1 (Control) | Group 2 (PXS) | *p* |
|---|---|---|---|
| ***N*** | **143** | **100** | |
| Neutrophil-to-lymphocyte ratio (NLR) | 1.43 ± 0.58 | 2.02 (1.33–2.66) | < 0.001 |
| Monocyte-to-lymphocyte ratio (MLR) | 0.16 ± 0.08 | 0.36 (0.24–0.50) | < 0.001 |
| Platelet-to-lymphocyte ratio (PLR) | 87.1 ± 35.1 | 130.8 (89–182.3) | 0.011 |
| SIII ($10^9$/L) | 398.6 ± 193.7 | 669.6 (440–1028.4) | < 0.001 |
| SIRI ($10^9$/L) | 0.73 ± 0.49 | 2.08 (1.03–3.12) | < 0.001 |
| SIMI ($10^9$/L) | 44.2 ± 21.44 | 117.04 (84.5–190.9) | < 0.001 |
| AISI ($10^{18}$/L) | 286.6 ± 122.4 | 641.6 (345.7–1017.7) | < 0.001 |

SIII: Systemic immune inflammation index (Platelet x Neutrophil) / Lymphocyte counts

SIRI: Systemic inflammation response index (Monocyte x Neutrophil) / Lymphocyte counts

SIMI: Systemic inflammation modulation index (Monocyte x Platelet) / Lymphocyte counts

AISI: Aggregate index of systemic inflammation (Monocyte x Neutrophil x Platelet) / Lymphocyte counts

PXS: Pseudoexfoliation Syndrome

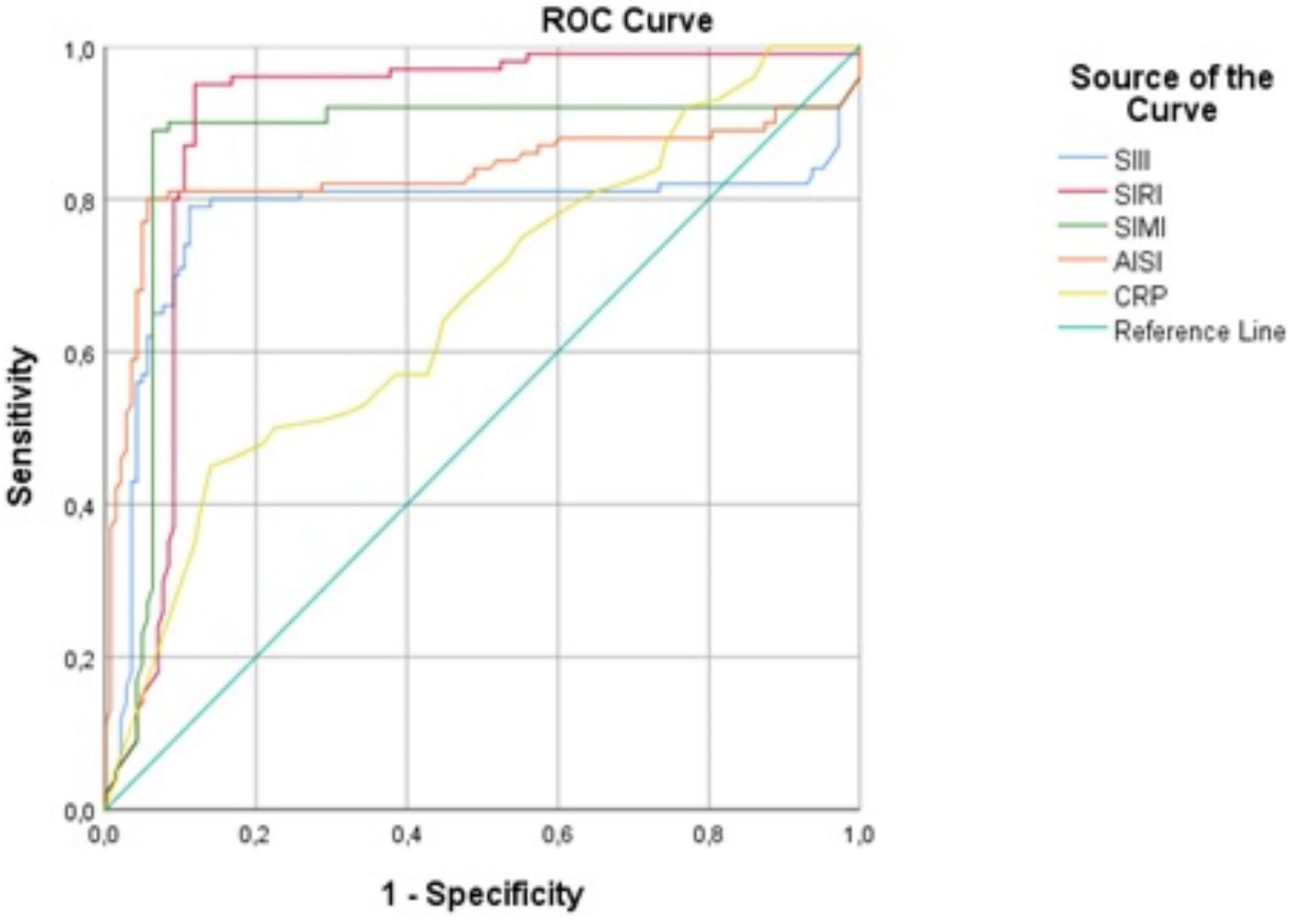


**Fig. 1** ROC graph of systemic immune indexes

**Table 5** ROC analysis data for systemic immune indexes

| | | | | Asymptotic 95% Confidence Interval | |
|---|---|---|---|---|---|
| **Test Result Variables** | **Area** | **Standard Error[a]** | **Asymptotic Significance[b]** | **Lower Bound** | **Upper Bound** |
| SIII | 0.776 | 0.038 | < 0.001 | 0.702 | 0.851 |
| SIRI | 0.897 | 0.023 | < 0.001 | 0.852 | 0.943 |
| SIMI | 0.865 | 0.030 | < 0.001 | 0.806 | 0.925 |
| AISI | 0.833 | 0.033 | < 0.001 | 0.769 | 0.897 |
| CRP | 0.563 | 0.085 | 0.084 | 0.494 | 0.633 |

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

SIII: Systemic immune inflammation index: (Platelet x Neutrophil) / Lymphocyte counts

SIRI: Systemic inflammation response index: (Monocyte x Neutrophil) / Lymphocyte counts

SIMI: Systemic inflammation modulation index: (Monocyte x Platelet) / Lymphocyte counts

AISI: Aggregate index of systemic inflammation: (Monocyte x Neutrophil x Platelet) / Lymphocyte counts

CRP: C-reactive protein

keratoconus patients have shown that SIII, NLR and PLR are higher in patients compared to healthy controls [16–20].

Yalınbaş Yeter et al. showed that MHR and NLR are simple and cost-effective biomarkers to predict diabetic macular edema and that high NLR may cause insufficient reduction in central retinal thickness after treatment [21]. Özarslan Özcan et al. investigated inflammatory status in dry eye syndrome patients using biomarkers. They reported that SIII, which is used as a new tool, may be a more reliable marker than NLR and PLR [22]. Kurtul et al. found that SIII, as a new index of inflammation, may be a more important tool than NLR and PLR in determining the severity of uveitis and may be a potential index in clinical practice to monitor and manage response to anti-inflammatory therapy in these patients [23].

All these literature data suggest that systemic immune indexes can be used to evaluate and monitor the inflammatory status in patients. Systemic immune indexes may provide new perspectives in understanding the pathophysiology of diseases affecting many tissues and systems, especially PXS, and in developing possible treatment methods.

There are many studies on the pathogenesis of PXS in the literature. In a study by Yıldırım et al. PXS patients were compared with healthy controls. The mean IL-6 level was found to be higher in the patient group compared to the control group [24].

In a study by Schlötzer-Schrehardt et al., both total and active TGF-β concentrations were significantly increased in the aqueous humor of PXS eyes and glaucoma compared to control eyes. Increased levels of latent and active TGF-β have been reported to support the formation of abnormal extracellular elastic material characteristic of PXS [25].

Elucidating the pathogenesis of PXS and predicting the complications that may develop in PXS eyes may make patient management more effective. Recognizing risk factors and identifying prognostic factors may improve patient follow-up. Systemic immune indexes are a set of inexpensive and simple criteria derived from peripheral blood. In PXS patients, the level of these parameters obtained from peripheral blood may provide insight into the course of the disease.

Vidal-Villegas et al. found that the levels of three cytokines were significantly different in the aqueous humor of primary open angle glaucoma patients (POAG) and pseudoexfoliation glaucoma (PXG). IL-12 and IL-13 were higher in the POAG, while monocyte chemoattractant protein-1 (monocyte chemotactic and activating factor) was higher in the PXG [26].

In a study investigating YKL-40, a protein involved in aqueous and chronic inflammation, there was a significant difference in mean aqueous humor YKL-40 levels in the PXS compared to the healthy control. The results of this study suggest that increased aqueous humor levels of YKL-40 are a local marker for inflammation in PXS patients [27].

In a similar study in the literature, both SIII and NLR were significantly higher in PXS patients. Compared to the control group, there was a statistically significant difference only in NLR in PXG patients [28].

In our study, leukocyte, monocyte and platelet counts were found to be higher in the PXS compared to healthy controls. NLR, MLR, PLR, SIII, SIMI, SIRI and AISI levels calculated with these parameters were also significantly higher in PXS patients compared to healthy controls. According to the results obtained, the presence of systemic inflammation in PXS patients can be mentioned. Systemic inflammation may be an indicator of intraocular inflammation and may also indicate systemic involvement of PXS. Prospective and large participatory studies are needed to understand the importance of the parameters and to estimate their power.

In the ROC analysis, SIRI and SIMI were found to be markers of higher significance among these parameters. These systemic immune indexes are calculated by a series of mathematical formulations based on cell counts obtained from peripheral blood samples. Since these indexes include multiple cell subtypes, they can provide more detailed information about disease pathogenesis. They may be useful in the follow-up of patients and may play a role in predicting complications.

All these findings and literature data suggest that inflammation may play a role in the pathogenesis of PXS. Moreover, these findings obtained from peripheral blood samples may be an indicator of multisystemic complications in PXS. It is noteworthy that monocyte count and monocyte activating factor were elevated in PXS patients in a study in the literature and in our study.

As known, platelets regulate monocyte function by modulating the activity and differentiation of monocytes [29, 30]. Activated platelets bind to monocytes and initiate the proinflammatory monocyte response [31, 32]. In addition, platelet-derived signals both directly and indirectly regulate the expression of proinflammatory cytokines. Activated platelets and platelet-derived microvesicles enhance monocyte activation and lead to the release of complement factor [33, 34].

In our study, monocyte count and SIMI -a newly defined index using monocyte count- were higher in PXS patients compared to healthy controls. This finding may give an idea for future studies to investigate the role of monocytes in the pathogenesis of the disease in PXS patients. Medications that regulate monocytes and/or monocytes-released factors from may be a treatment option in PXS patients in the future. Another perspective is that treatment response in PXS patients could be assessed using systemic immune indexes such as monocyte count or SIMI.

Among the limitations of our study, the impact of these systemic immune indexes on prognosis could not be assessed because it was a cross-sectional case-control study. Although other clinical manifestations of active infection are exclusion criteria, the impact of asymptomatic disease may have influenced the findings. Furthermore, the contribution of pseudoexfoliation to the development of pseudoexfoliation glaucoma in PXS patients could not be analyzed. The strengths of our study include the fact that it is one of the first studies to investigate several systemic immune indexes in PXS patients, including SIRI, AISI and a newly described index, the systemic inflammation modulation index (SIMI).

In conclusion, systemic immune indexes (NLR, MLR, PLR, SIII, SIRI, AISI and SIMI) were elevated in PXS patients compared to healthy controls. These indexes may serve as an easy, simple and cost-effective tool to assess the degree of systemic inflammation in patients, playing an important role in recognizing the underlying mechanisms of diseases and thus potentially guiding treatment.

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**Author contributions**
ÖÖ: the main idea of the research, design, collection data and critical review ESG: literature review, writing and review. All authors reviewed the manuscript.

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**Data availability**
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

## Declarations

**Ethics approval and consent to participate**
The protocol of our study was approved by the Toros University Scientific Research Ethics Committee (May 23, 2024/106). Written informed consent was obtained from all participants.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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## Publisher's note